Registration of mixed formulations of pesticides†

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Abstract: Applying pesticides in mixture can bring about an increased level of performance which can be of benefit to manufacturers who make use of this phenomenon when formulating products. The interactions that occur can also bring about adverse effects on performance and possibly on the safety of the product to users, consumers and the environment. Because of this a product containing a mixture of active substances must be considered by registration authorities. Each discipline in the regulatory process must consider the likelihood of an interaction occurring and, as a result, request and examine the necessary data to support approval for that mixed product. Within the European Community the requirements are laid down in Directives that have been introduced to harmonise the regulatory process across Member States. The requirements of these Directives are described as an example of the regulatory process.

Keywords: pesticides; antagonism; synergy; regulation; registration

1 INTRODUCTION

A pesticide formulation contains one or more pesticides together with many other components such as materials to stabilise the formulation or increase pesticide uptake, dyes and antifreeze. There can be a range of interactions between these components. The purpose of this paper is only to consider the interactions between pesticide active substances when they are contained in the same formulation and how this relates to the pesticide registration requirements for approval of such a formulated product.

In order to understand the regulatory concerns that might apply to mixed formulations of pesticides, the European Community (EC) scheme will be taken as an example. UK legislation states that the reason for regulating pesticide use is to protect the health of human beings, creatures and plants, to safeguard the environment and to secure safe, efficient and humane methods of controlling pests.[1] To address each concern, the necessary data are examined, the process generally being the same with formulated mixtures of pesticides as it is for products containing a single active substance.

Within the EC, harmonisation of the controls over plant protection products has been introduced; a Directive known as the 'Authorisation Directive' (Council Directive 91/414/EEC) laid down the basic framework for the harmonised controls.[2] This introduced a two-stage system which came into operation on 26 July 1993. The UK has introduced the Plant Protection Product Regulations 1995 to implement controls over pesticides in line with the Directive.[3]

2 SAFETY CONCERNS

Central to the EC harmonised evaluation of pesticide authorisations has been the laying down of data requirements for each area of concern and the principles by which these data shall be evaluated by Member States.

2.1 Mammalian toxicology

Initially, when an applicant wishes to register a formulation containing more than one active substance, the standard acute toxicity package with the new formulation is considered. If the acute toxicity of the new formulation is not significantly different from that which would be estimated from its individual components, it is unlikely that further mammalian toxicity data on potential interaction would be required. Use of calculation, as an alternative to submission of acute data, may be permissible where tests are available on similar formulations. Calculation may also be permissible where there is no evidence from other toxicological data that classification on such a basis would be inappropriate.

However, consideration of acute toxicity alone may not be appropriate for certain combinations of active

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substances where the mechanism of chronic toxicity may be altered by co-application, such as when one of the compounds affects metabolism of other compounds. In such a case, or where the results of acute toxicity tests on the formulation indicate that an interaction is occurring, then further data may be required. Requirements may include, for example, data to reveal any possible alteration of mammalian absorption, distribution, excretion and metabolism of the active substances as a result of co-administration. Data may be needed to reveal any possible alteration of the mammalian toxicity of the active substances caused by co-administration. Suitable endpoints based on knowledge of the toxicological profiles of the active substances would need to be selected.

An example of the significance of potential additive effects of combining two pesticides is the restriction in the UK on the mixing of two products containing anticholinesterase compounds. Generally the Admissible Operator Exposure Levels (AOEL) for such compounds are based on cholinesterase inhibition. Therefore it is possible that using one product containing an anticholinesterase compound could 'use up' all the AOEL and if two such products were combined the AOEL may well be exceeded. Hence, unless a risk assessment has been conducted that demonstrates a lack of effect for such a use, the restriction applies.

2.2 Residues

In general, it is taken that active substances act independently and do not interact unless there is knowledge to suggest that they do. For mixed formulations, if residue data are being generated for both/all the active substances in the formulation, then it is likely that a mixed formulation would be applied and so any possible interactions would be taken into account. However, in cases where one of the active substances in a mixed formulation is already registered and the other is new, a case for extrapolation from another formulation for the existing active may be possible and new data need only be generated for the new active substance. The data for the new active substance would of course take into account any influence the registered active had on the new one, assuming the mixed formulation was applied in the trials. There are cases where a claim is made that the use of one active substance can directly affect the uptake and movement of another. If these active substances are formulated together, then metabolism and residue data are needed for each component. For example, it is claimed that imazaquin can increase the uptake, and therefore the effectiveness, of chlormequat as a plant growth regulator.[4] It would need to be shown that the combined treatment did not give rise to unacceptable residues of chlormequat.

For particular areas of concern combined residues of similar active substances can be considered. However, these residues may well arise from active substances being applied separately to the plant in a sequence of applications rather than from them being applied in mixtures.

2.3 Ecotoxicology

Ecotoxicology data requirements for formulated products are contained in Section 10 of Annex III of the Authorisations Directive (Commission Directive 96/12/EC).[5] Data on the acute toxicity of any formulation to aquatic species are needed if it is not possible to predict its toxicity using active substance data. It is stated that this is especially the case if a product contains two or more active substances. Testing on bees and other non-target arthropods, as well as earthworms, may also be required for mixed active substance products. These data on the product can then be fed into the risk assessment for its proposed use, and any appropriate regulatory action taken.

2.4 Operator exposure

Exposure of operators to pesticides is measured or calculated from predictive models. It is not considered that applying pesticides together will increase the exposure to the individual active substances applied. The interactions that may occur if exposure to both active substances occurs are discussed in Section 2.1 above.

2.5 Fate and behaviour

In the assessment of the fate and behaviour of pesticides in the environment it is considered that active substances do not normally interact and so each active substance applied is considered separately. In general, formulation-specific data are only required on slow-release formulations, so if the mixture were formulated in this manner then further data on the fate and behaviour of each of the active substances would be required.

2.6 Physicochemical properties

Data are required to be submitted on the physical properties of any new formulation, including those containing more than one active substance. These properties must be measured before and after storage to demonstrate that the product can be applied in the way recommended, ie for a spray, that a product dissolves or disperses in the spray tank and will pass through nozzles. The full data requirements are given in Commission Directive 94/37/EC.[6]

3 EFFICACY

It is common practice for producers of agrochemical products to seek approval for formulations containing two or more active substances, as they can offer several advantages, some of which relate to performance, eg improvement in crop safety or effectiveness.

The effect on efficacy of mixing active substances together has been studied in detail and there is a wide range of published information available, sum-

marized by Hatzios and Penner.[7] Herbicides active against grass weeds seem particularly prone to antagonism. For example, the aryloxyphenoxypropionates, or 'fops' have long been known to be antagonised by the phenoxycarboxylic acids, or hormone herbicides.[9] Negative interactions continue to be a problem with the most recently released herbicide for grass weed control in the UK, flupyrsulfuron, being reported to be antagonised by isoproturon.[9] It is also apparent that biological incompatibility is relatively rare in mixtures which do not involve herbicides or plant growth regulators.[7]

Positive effects can result from mixing two or more active substances. However, many mixtures are based on an additive effect rather than synergy. These positive and negative interactions can result in an impact both on the control of the target pest and on the safety to the crop. Consequently, it is particularly important in the area of efficacy that specific data are supplied on products containing more than one active substance, rather than simply relying on data provided on the two active substances when applied separately.

3.1 Data requirements

The detailed requirements for the efficacy testing that is required are given in Commission Directive 93/71/EEC.[10] As many of the areas of assessment are product-related, they therefore apply to formulations containing more than one active substance. The requirements cover: effectiveness, including dose justification; crop safety or phytotoxicity, including yield; and other factors such as resistance and effects on succeeding crops.

3.2 Extent of testing

Where a product contains a mix of active substances, the biological evidence required is dependent on the claims made on the label and the doses of the active substances recommended. There are two common scenarios:

(a) Where the synergy or additivity of the two active substances is deliberately exploited. This will mean that either the doses of the active substance(s) are decreased or the claims made on the product label are increased, when compared to the label and dose of the constituent active substances applied alone. The data requirements will be the same as those for a similar recommendation using a product containing a single active substance. This will normally comprise at least 10 crop safety trials and 10 trials per major pest carried out over two growing seasons. For less important pests and related minor crop, less testing will be required. For herbicides, application at double the recommended dose must be made in the crop safety trials.

(b) Where the active substances are being formulated together for convenience. This means that the doses of active substances applied in the mixture are the same as the dose of the constituent active substances when applied alone and label claims are similar. In this instance, a reduced set of efficacy data designed to show lack of antagonism is likely to be acceptable.

Thus a total of five appropriate trials, where both effectiveness and crop safety of the mixture are assessed in comparison to the constituent active substances on a selected range or target species and crops claimed on the label is required. This should be sufficient to confirm that no unforeseen interactions will occur. Where results of such trials show unacceptable interactions a full programme of trials may be required, eg if increased levels of phytotoxicity occur then dedicated crop safety trials including yield results may be necessary.

The above comments assume that there is a full supporting data package on each individual constituent active substance.

3.3 Other factors (eg resistance and effects on succeeding crops)

All the efficacy requirements given in Directive 93/17/EEC must be addressed for any products, including mixtures.[10] However, in the majority of cases, extrapolation from the existing data on the constituent active substances should suffice. Careful consideration must, however, be given to each area of concern to ensure that there will not be unforeseen interactions, eg the risk to succeeding crops could be increased if two active substances with the same activity against succeeding crops were both applied at recommended doses. The use of mixtures has been claimed as a positive tool in managing resistance to pesticides. However, caution must be exercised, as the mixing of two active substances does not always provide the answer to resistance problems, ie if the same pests are not controlled by the two active substances or the two active substances have similar modes of action.[11]

4 CONCLUSIONS

There are known interactions between pesticides. Where there is an indication that they may cause negative effects on humans and non-target species these interactions need to be investigated and the risk assessment needs to be adjusted. They also need to be assessed to ensure that the crop treated by the product is not adversely affected nor is the effectiveness of the product reduced.

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